Remarks and Arguments

Claims 32, 35, 40, and 45, have been amended. Support for the amendment to claim 32 can be found at least in paragraphs 6, 11, and 54 of the application as published. Claims 39, 43, 44, 48-51 have been canceled. Support for new claim 52 is found in at least paragraph 13 of the application as published, and support for new claim 53 is found in at least paragraph 14 of the application as published. It is believed that no new matter has been added.

A. Background

The pending claims stand rejected over U.S. Patent 6,443,976 to Robert W. Flower et al. (hereinafter "the '976 patent") and WO/0047107 to Pang et al. (hereinafter "the '107 application").

Independent claim 32 is drawn to a method of treating a lesion. This method is particularly effective because the treatment composition is caused to be concentrated in the lesion. The following is explained in the current application as published (emphasis added):

> [0011] The present invention provides a more effective method for treating lesions, in an animal... The method of the present invention utilizes photocoagulation and PDT methodologies.. . .
>
> [0016] One advantage of the present invention is that by cutting off the blood flow using photocoagulation or DEP after administration of the PDT agent, the PDT agent becomes incarcerated in the lesion. **This is significant as PDT agents, such as Visudyne.TM., were previously thought to be held in the lesion during treatment because they were selectively bound to lesion tissues. However, it has come to light that PDT agents may not be as selectively bound to lesion tissues, such as CNVs, as originally anticipated. Therefore, by cutting off the blood flow to the lesion, once it has become at least partially filled with PDT agent, the PDT agent is physically held in the lesion for and during PDT.**
>
> [0017] A further advantage is that the incarceration of the PDT agent in the lesion also allows the PDT agent in non-lesion areas to be flushed out at higher flush-out rates as compared to lesion areas. As a result, non-

lesion areas will be subjected to less PDT mediated damage while maintaining PDT agent in the lesion area.

[0018] A still further advantage is that the incarceration of PDT agent in the lesion increases the concentration of PDT agent in the lesion during treatment. A higher concentration of PDT agent in the lesion allows for more effective treatment.

[0019] A still further advantage is that given that the PDT agent can be effectively concentrated in the lesion, the overall amounts of PDT agent used can be lowered. In the instance where PDT agent is infused, infusion time can therefore be correspondingly lowered. This is economically advantageous and decreases the likelihood of side effects resulting from the PDT agent.

[0020] A still further advantage is that the reduction of blood flow through the feeder vessel enhances the rate of PDT-induced clot formation during PDT by reducing the movement and flow of blood through the lesion.

For reasons that will be explained below, neither of the '976 patent nor the '107 application teach the steps required to obtain the desired result of concentrating the treatment composition in the lesion. Further, neither reference reveals the problem solved by the pending application (i.e., that the PDT agent is not selectively bound by lesions and hence flows into and out from lesions), and in fact they teach away from this Hence, there is absolutely no motivation for the skilled artisan to invent the methods of the invention starting from either the '976 patent nor the '107 application. Each of these points will be addressed in more detail below.

B. The '976 Patent does not anticipate claim 32 and in fact teaches away from the invention of claim 32.

1. The '976 patent does not anticipate independent claim 32.

Claims 32 and 37-51 are rejected as being anticipated by the '976 patent. In particular, the Examiner argues that the '976 patent teaches both PDT and photocoagulation, and that these can be performed in any order. It is respectfully

submitted that the '976 patent does not anticipate the pending claims for the reasons stated below.

Specifically, to anticipate a claim, a reference must teach every element of the claim (MPEP Section 2131). A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "*

A patent **claim** is anticipated if each limitation is described, either expressly or inherently, in a single prior art reference. In addition, the reference must be enabling and describe the applicant's claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." In re Paulsen, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994). Moreover, "every element of the claimed invention must be literally present, arranged as in the **claim,**" and the prior art must show the "**identical invention . . . in as complete detail as is contained in the** patent **claim."** *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989; emphasis added). The absence from a prior art reference of any claimed element of the patented invention negates anticipation. *Kloster Speedsteel AB v. Crucible, Inc.*, 793 F.2d 1565, 1571 (Fed. Cir. 1986).

First, the '976 patent does not disclose the steps of claim 32 in the particular sequence of this claim. It does not disclose a method by which there is a reduction of the rate by which the treatment composition exits a lesion prior to application of energy to the lesion that is sufficient to excite photodynamic agent. The '976 patent discloses steps for performing two self-contained and temporally distinct therapies, namely a PDT therapy method and a photocoagulation therapy method. The PDT therapy method is defined as "administration of a photodynamic dye into a subject. . .[and subjecting] the dye . . . to radiation . . .causing excitation of the dye" (col. 1, lines 43-53). The photocoagulation therapy method is "subjecting a blood vessel that carries blood into the lesion to thermal photocoagulation to reduce the flow of blood through that vessel and into the lesion" (col. 2 lines 30-34).

The '976 patent clearly states that these two therapeutic methods are intended to be self-contained, temporally distinct methods (emphasis added):

> Another aspect of the present invention provides methods specific to the treatment of a CNV. **In connection with the development of this aspect, it was recognized that, after PDT of a CNV was completed, and recurrence of the CNV was detected, angiograms of the CNV permitted CNV feeder vessels to be readily identified, as compared to angiograms obtained without prior PDT. Of course, once such feeder vessels are identified, thermal** photocoagulation (with or without the use of a radiation-absorbing dye, the latter also referred to as dye enhanced thermal photocoagulation) **can be performed with a relatively high degree of success, providing for relatively permanent treatment of the CNV** (col. 2 last paragraph).
>
> . . .
>
> "It should be appreciated that the further treatment step of thermal photocoagulation is preferably performed after the application of PDT when reperfusion of the CNV is detected, but it is not intended that the inventive methods be limited to that sequence. **If reperfusion after PDT occurs, it typically is detectable 2-8 weeks after PDT.** Thus, PDT and thermal photocoagulation need not be performed during a single treatment session. Days, or more likely weeks, could separate the PDT and thermal photocoagulation steps without departing from the spirit and scope of the present invention. (col. 6 second full paragraph).

Thus, the '976 patent teaches that the PDT method and the photocoagulation method should be performed 2-8 weeks apart, and necessarily that the two treatments hence are practiced separately from each other.

Claim 32, on the other hand, *requires* the steps of the photocoagulation and PDT methods be combined with each other. In particular, a photocoagulation step is interposed between a step of administering a PDT agent and a step of irradiating the PDT agent. In particular, claim 32 requires (emphasis added):

PDT or Photocoagulation	Claim Language (emphasis added)
PDT	"(ii) administering a treatment composition comprising . . . a photodynamic agent . . . "
Photocoagulation	"(iii) **after step (ii),** applying energy to said blood vessel, of a type and in an amount sufficient to reduce the rate of blood flow through said blood vessel"
PDT	"(v) **after step (iv),** applying energy to said lesion, of a type and in an amount sufficient to excite said photodynamic agent"

Further, it is believed that the '976 patent does not disclose the step of "administering a treatment composition comprising a fluorescent dye and a photodynamic agent . . . " as required in amended claim 32.

The Examiner argues that the '976 patent teaches the invention of claim 32 because it states that "[i[t should be understood that these methods and associated steps may be performed in any logical order" (Col. 3 lines 36-37). Applicant respectfully disagrees. The Applicant cannot find any teaching in the '976 patent that the steps of the PDT and photocoagulation methods should be combined during a single treatment procedure in the precise order claimed. Such reading is clearly contrary to the intention and teachings of the '976 patent as described above, and would involve impermissible hindsight on the part of the Patent Office to interpret the '976 patent contrary to its explicit teachings.

Hence, the '976 patent does not teach all the claim limitations of claim 32 of the present invention. There is no teaching whatsoever in the '976 patent to intermix the steps of the PDT and photocoagulation methods such that the steps of claim 32 are anticipated. It does not teach "[t]he identical invention . . . in as complete detail as is contained in the ... claim" as required by Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). For this reason, it is respectfully submitted that the '976 patent does not anticipate claim 32 of the pending application.

2. The '976 patent teaches away from the invention of claim 32

Further, it is respectfully submitted that there is no motivation whatsoever in the '976 patent to make the invention of the present application. As stated above, the present invention indicates the following problem and solution:

> PDT agents may not be as selectively bound to lesion tissues, such as CNVs, as originally anticipated. Therefore, by cutting off the blood flow to the lesion, once it has become at least partially filled with PDT agent, the PDT agent is physically held in the lesion for and during PDT.

The '976 patent not only fails to recognize the problem that PDT agents may not selectively bind to lesion tissues, but in fact incorrectly states that PDT agents DO bind to lesions. It states (emphasis added):

> Common methods of treating abnormal vasculature use laser technology. One example of such methods, used in the treatment of CNV, is photodynamic therapy (PDT). The object of PDT is to permit selective destruction of undesirable tissue without damaging surrounding healthy tissue. **This is possible because the photodynamic dyes used in PDT are selectively retained in the area to be treated. For example, in the case of CNV, the photodynamic dye selectively binds to the proliferating endothelium in the CNV** (col. 1 lines 29-37).

Thus, the '976 patent expressly teaches away from the invention of the pending application. To the extent that the '976 patent depends from a fundamental misconception that PDT dye automatically binds to the CNV, it is submitted that the skilled artisan would not even understand the problem to be solved, much less the solution to this problem.

C. Claim 32 is not obvious over the '107 application in combination with the '976 patent

1. The '107 Application does not overcome the inadequacies of the '976 patent in teaching or motivating the invention

Claims 32-32 and 37-51 are rejected under 35 U.S.C. § 103 as being unpatentable over the '107 application in view of the '976 patent. Applicant traverse(s) this rejection on the grounds that the Examiner has failed to create a *prima facie* case of obviousness. In accordance with MPEP §2143.03, to establish a prima facie case of obviousness 1) the prior art reference (or references when combined) must teach or suggest all of the claim limitations; 2) there must be some suggestion or motivation to modify a reference or combine references; and 3) there must be a reasonable expectation of success.

As stated above, the '976 patent does not teach or motivate all of the claim limitations of independent claim 32. The '107 application does not cure any of these deficiencies, and is at best merely cumulative over the '976 patent.

Similarly to the '976 patent, the '107 application does not teach the step of "administering a treatment composition comprising a fluorescent dye and a photodynamic agent . . .", nor does it teach the sequence of steps required by amended claim 32.

Further, like the '976 patent, the '107 application teaches that the photocoagulation and PDT methods are separate and distinct. In particular, on page 20, lines 10-30, it teaches that the treatment sequence involves injecting dye (lines 24-25) and firing the treatment laser (lines 26-28). Similarly, the PDT sequence involves injecting dye and irradiating it (page 23 lines 31-35). There is no teaching in the '107 application to administer the steps of the PDT method and the photocoagulation method as anything but self-contained methods.

Like the '976 patent, this reference presents a fundamental misconception as to the affinity of PDT agent to CNV lesions. The '107 application teaches that indocyanine green dye (ICG) stains choroidal neo-vascular membranes (CNVM) (page 12 lines 15-17), stating:

> While executing this procedure of analysing fluorescein early filling, the second marker, ICG is staining the vessel walls of the CNVM.

As such, the skilled artisan would have no motivation to combine the separate procedures (PDT and photocoagulation) in the sequence required by claim 32, because the skilled artisan would be relying on the notion that the PDT agent would be inherently self-contained with the lesion. Therefore, the skilled artisan would be incapable of recognizing the underlying problem that needs to be solved, much less the solution to be found to such a problem.

2. The '107 application is not enabled, and would lead the skilled artisan away from conceiving the invention of the pending application

MPEP 2121.01 states in relevant part:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'... ." *In re Hoeksema,* 399 F.2d 269, 158 USPQ 596 (CCPA 1968). The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. **>Mayo Found. For Med. Educ. & Research<*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003)
>
> . . .

II. 35 U.S.C. 103 REJECTIONS AND USE OF INOPERATIVE PRIOR ART

> "Even if a reference discloses an inoperative device, it is prior art for all that it teaches." *Beckman Instruments v. LKB Produkter AB*, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989). Therefore, "a non-enabling reference may qualify as prior art for the purpose of determining obviousness under 35 U.S.C. 103." *Symbol Techs. Inc. v. Opticon Inc.*, 935 F.2d 1569, 1578, 19 USPQ2d 1241, 1247 (Fed. Cir. 1991).

The '107 application is full of cryptic comments and inconsistencies that would likely confuse the skilled artisan and lead him away from conceiving the invention of the present application.

As an example, the '107 application includes technical absurdities as to the size of the laser spot that might be used to treat the human eye. On page 12 lines 26-31 it states:

> A (100(m laser spot of appropriate power is aimed directly at the suspected feeder(s) and the treatment mode (photocoagulation) is executed. Preferably, the laser spot size should be between (50(m and (100(m to adjust to the expected cross-sections of the feeder vessels.

This is highly confusing given that the human eye is no more than several inches in length and the treatment laser is designed to damage human tissue. It is not likely that a doctor would consider it acceptable to irradiate a human being with a 100m or 50m laser spot that is designed to damage tissue if the goal is to treat a small area of the eye.

The '107 application also includes wholly contradictory statements as to how ICG dye should be used. For example, on page 8 line 37 – page 9 line 8 it states (with emphasis added):

> Disease spots are stained by ICG in the longer term (e.g. of 3-5 minutes post-injection). By then superimposing flouroscein stills on the live, evolving ICG staining, and focusing on the thin layer about the spot (**so as not to excite the ICG**, which may still be coursing through the normal choroidal and retinal vasculature--but which would be out of focus in the

confocal system), the disease spots can be confirmed, targeted and treated.

However, each of the ICG sequence, (page 18 lines 11-12), the treatment sequence (page 20 lines 24-29) and the PDT sequence (page 23 lines 24-25) teaches irradiation within the excitation range of ICG, which is between about 700 and 820nm according to Figure 1 of the ICG dye NDA that was downloaded from the FDA website and is attached hereto as an Exhibit. Variations "A", "B" and "C" of the ICG sequence on pages 18-19 disclose administration of ICG but do not disclose how it can be made visible so as to achieve the goals of the invention.

The '107 application is further wholly inconsistent as to the power levels that should be used to irradiate ICG dye. It states on page 21 line 8 – page 22 line 3 (emphasis added):

PHOTO-DYNAMIC THERAPY

A sequence similar in procedure to Photo-Dynamic Therapy (PDT) can be inserted at the end of the Treatment Sequence.

. . .

PDT uses the photo-chemical effect of a photo-sensitizer chemical which concentrates or is selectively absorbed in the pathological neo-vascular vessels. The photo-sensitizer does not stain or only minimally concentrates in healthy areas.

. . .

ICG can be analogously considered as such a photo-sensitizer in our application. The principal difference is that ICG does not release "free radicals" or such. It operates with low a purely thermal effect. **Like PDT, the ICG is similarly exposed to power irradiation (<50 mW, for**

example). The value is not exactly known (depending on the staining, the optics and the ocular media).

> The ICG excitation IR illumination is close to or can be the same as the treatment laser wavelength (or waveband) (This is because the overlap of ICG excitation and ICG fluorescence wavebands is relatively large. Each waveband, by itself, spans more than 100 nm.) The difference between illumination and treatment beams is that the continuous illumination is at much lower power and/or is much more diffused; **while the treatment beam is much more focused (<(100(m treatment beam spot) and at much higher pulsed powers (up to 2000 mW).**

This large range in power levels is highly confusing, given that power is understood to refer to energy as a function of time. See, for example, the Wikipedia page for "Power" at http://en.wikipedia.org/wiki/Power_%28physics%29.

Hence, there is no teaching in the '107 application that would lead the skilled artisan to conceive the invention of the present application. At best, the '107 application is merely a confusing reference that adds nothing to the teachings of the '976 patent.

D. The dependent claims are novel and inventive

All pending claims dependent claims depend directly or indirectly from claim 32, and hence necessarily incorporate the limitations of claim 32. It is believed that each of these claims are novel and inventive at least for the same reasons as apply to claim 32.

RECONSIDERATION

It is believed that all claims of the present application are now in condition for allowance.

Reconsideration of this application is respectfully requested. If the Examiner believes that a teleconference would expedite prosecution of the present application the Examiner is invited to call the Applicant's undersigned attorney at the Examiner's earliest convenience.

Any amendments or cancellation or submissions with respect to the claims herein is made without prejudice and is not an admission that said canceled or amended or otherwise affected subject matter is not patentable. Applicant reserves the right to pursue canceled or amended subject matter in one or more continuation, divisional or continuation-in-part applications.

To the extent that Applicant has not addressed one or more assertions of the Examiner because the foregoing response is sufficient, this is not an admission by Applicant as to the accuracy of such assertions.

Please grant any extensions of time required to enter this response and charge any fees in addition to fees submitted herewith that may be required to enter/allow this response and any accompanying papers to our deposit account 02-3038 and credit any overpayments thereto.

Respectfully submitted

/inna landsman/ Date: November 5, 2007

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